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EXAMINER	
FORD, ALLISON M	

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1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,641	HAKAMAZUKA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 8-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment of 23 September 2003, canceling claims 1-7 and submitting new claims 8-27 has been entered. Claims 8-27 are pending in the current application, all of which have been considered on the merits.

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C 365(c) as a continuation of PCT/JP02/02744, filed 22 March 2002, which further claims priority to Japanese national application 2001-084525, filed 23 March 2001. It is noted, however, that applicant has not filed a certified translation of PCT, which has been published in the Japanese language. Without a certified translation it cannot be verified that the instant application is a proper continuation, as such priority is not granted at this time and the effective filing date of the claims, for purposes of applying art, is considered to be 23 September 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants claims are directed to an artificial bone material comprising a porous ceramic consisting of beta-tricalcium phosphate and a marrow cell incorporated into the porous ceramic, as well as a method for producing said artificial bone material.

Initially, it is not clear what applicant intends by "a marrow cell." Marrow, presumably bone marrow, comprises a number of different cell types, including hematopoietic stem cells, mesenchymal stem cells, and the various progenitor and mature cells descending from each of the stem cell types. Therefore, it is not clear which of the cell types, which are found in bone marrow, is intended to be claimed within the composition.

In claims 12, 13, 21 and 22 the phrase "macropores...that communicate to each other" is unclear; it appears applicants are intending for the macropores to be interconnected, in all of claims 12, 13, 21 and 22 it would be remedial to claim "...wherein the porous ceramic has a porosity of 60% to 90%, and includes interconnected macropores of size 50 um to 1000 um, and micropores of size 2 um or less."

In claim 18 depends from claim 8; however, it appears it should depend on claim 17, as it references the incubation step of claim 17.

It is further noted that claims 16-19 do not lend patentable distinction to the product of claim 8, as each of claims 16-19 are directed to steps of producing the artificial bone material, but do not add structural limitations which affect the patentability of the material, per se.

In claim 23 the limitation "the incubation" lacks proper antecedent basis, as parent claim 20 does not include an incubation step or an incubation period.

In claim 25, again the limitation "the incubation" lacks proper antecedent basis, as parent claim 20 does not include an incubation step or an incubation period.

In claim 26 the limitation "the cultured cells" lacks antecedent basis, as parent claim 20 does not require the marrow cell to be cultured.

Furthermore, in claim 26, it is not clear how a cell is 'inoculated' under the conditions listed, rather it appears applicant intended to require the cells to be *incubated* under at least one of the listed conditions.

With regards to claim 27, it is not clear if the claim is to depend on claim 13 (as stated), wherein claim 13 is a product claim, not a method, or if claim 27 is to depend on claim 20. For purposes of examination, claim 27 will be considered to depend from claim 20.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8, 11, 12, 16-22 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by each of Bucholz (Clin Ortho Rel Res, February 2002) and Erbe et al (Eur Spine J, October 2001).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Applicants claims are directed to an artificial bone material comprising a porous ceramic consisting of beta-tricalcium phosphate and a marrow cell incorporated into the porous ceramic, and methods of making said artificial bone material. It is noted claims 16-19 depend from the product claim 8, yet they recite limitations directed to the method of producing the bone graft material, not to the bone graft material, per se, thus the claims are considered product-by-process claims. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the

product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Bucholz and Erbe et al each characterize the bone graft substitute material Vitoss™ (Orthovita, Inc, Malvern, PA). Vitoss is a porous, pure beta-tricalcium phosphate scaffold intended for use in bone graft generation for repairing osseous defects. Vitoss is made from lightly fused particles of beta-tricalcium phosphate averaging 1-2um in diameter, resulting in a highly porous (90%), low-density scaffold. The scaffold exhibits interconnected macro- and micro-porosity, wherein the macropores range in size from 100 to 1000 um, and the micropores range from 1 to 100 um (See Bucholz, Pg. 47; Erbe et al, Pg. S143).

Both Bucholz and Erbe et al further disclose a composite graft made using the Vitoss scaffold, which is formed by incorporating marrow into the pores of the scaffold, thereby forming an artificial bone material comprising a porous ceramic scaffold and marrow cells, wherein the ceramic scaffold consists of beta-tricalcium phosphate. It is noted that any marrow must inherently be obtained from a patient (Claims 8, 11, 13, 16-22, 27). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Bruijn et al (EP 0987032), in view of Hakamazuka et al (JP 01-108143), Muschler (WO 99/59500), and Klein-Nulend et al (J Cell Physiol, 1995).

Applicants claims are directed to an artificial bone material comprising a porous ceramic consisting of beta-tricalcium phosphate and a marrow cell incorporated into the porous ceramic, as well as a method for producing said artificial bone material.

Porous ceramic scaffolds used for generating artificial bone are known in the art. de Bruijn et al teach ceramic materials that exhibit both biocompatibility and biodegradability are suitable for development of a porous scaffold material. Specifically de Bruijn et al disclose beta-tricalcium phosphate as a preferred ceramic material (See de Bruijn et al, col. 2, ln 20-25). De Bruijn et al teach the beta-tricalcium phosphate scaffold exhibits macro- and microporosity, wherein the macropores preferably have a size of between 0.2 mm and 1.0 mm (200um to 1000 mm), and wherein the micropores preferably have a size of between 0.05 um and 20 um. De Bruijn et al teach the macro- and micropores are interconnected, and the overall porosity is between 20% and 90%, preferably between 40% and 70% (See de Bruijn et al, col. 2, ln 26-46). Please note, that while the ranges taught by de Bruijn et al are not identical to those currently claimed, the prior art ranges do significantly overlap the claimed ranges, and it has been held that in cases where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990). (Claims 11-13, 16).

Methods of producing such porous ceramic scaffolds for use in generating artificial bone were known at the time of the invention, for example, de Bruijn et al disclose the ceramic beta-tricalcium phosphate scaffold can be produced by sintering (See d Bruijn et al, col. 3, ln 6-14), further detail on the production process is found in Hakamazuka et al, where they specifically teach synthesizing tricalcium phosphate via a mechano-chemical process, then molding a slurry of calcined and ground synthetic TCP and an aqueous solution of ammonium polyacrylate, drying, and sintering at high temperatures (See Hakamazuka et al, abstract). Thus, in addition to the teachings of de Bruijn et al, it would have been obvious to one of ordinary skill in the art to look to Hakamazuka et al for additional guidance on the

specifics of forming a beta-tricalcium scaffold, as both references are concerned with formation of beta-tricalcium ceramics for use in bone regeneration. Because both references are directed to solving the same problem, and involve the same process of sintering, one would expect success following the more explicit teachings of Hakamazuka et al to produce a porous beta-tricalcium scaffold useful in the method of de Bruijn et al. (Claims 21, 22, 24).

It is noted that de Bruijn et al do not add cells to their scaffolds *ex vivo*, but rather appear to implant the scaffolds in an acellular state so that natural bone forming cells may invade and colonize the scaffolds. While de Bruijn et al do report some success regenerating bone *in vivo* in this manner, it alternatively would have been obvious to one of ordinary skill in the art, at the time the invention was made, to colonize the scaffold of de Bruijn et al *ex vivo* with cells prior to implantation. Clearly in situations where the intent is to regenerate or repair human bone defects, inclusion of cells in the implant is desirable, as the cells express additional growth factors, and reduce the need for chemotaxis of autologous osteoblast progenitor cells to the defect site, thus one of ordinary skill in the art would have been motivated to culture cells on the scaffold of de Bruijn et al.

One would have expected success in culturing cells on the scaffold of de Bruijn et al to form an improved artificial bone material for implantation because methods of culturing cells on ceramic scaffolds for the purpose of artificial bone formation were known in the art, see for example, Muschler. Muschler teaches methods for culturing cells, specifically cells from bone marrow aspirate obtained from a patient, on an implantable scaffold to form an artificial bone graft (See Muschler, Pg. 2, ln 20-27). Muschler teaches the scaffold may further have growth factors which contribute to osteogenesis, including bone morphogenic proteins, fibroblast growth factors, insulin-like growth factors, and platelet-derived growth factors (See Muschler, Pg. 5, ln 1-6). (Claims 8-10, 14, 15, 17-20, 23, 27).

Still further, in order to further optimize the artificial bone material of de Bruijn et al, it would have been further obvious to one of ordinary skill in the art to subject the cell-seeded scaffold to

mechanical loading (mechanical stimulation). It was known at the time the invention was made that application of mechanical strain on bone cells affects the growth and development of the tissue. Specifically, Klein-Nulend et al disclose application of intermittent hydrostatic compression by 13 kPa to *in vitro* mouse calvariae increases bone formation and decreases bone resorption, as well as affects the production of local growth factors (See Klein-Nulend et al, Pg. 116, col. 1). Therefore, in order to increase bone formation, for the purpose of providing the most suitable bone material for implantation, one of ordinary skill would have been motivated to apply mechanical stimulation to the cells during the culture period; one would have expected success because Klein-Nulend et al provide evidence of improved bone tissue quality with such stimulation. (Claims 25, 26).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1651